FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Meeting of the Oncologic Drugs Advisory Committee (ODAC)
FDA White Oak Campus, Building 31, the Great Room (Rm. 1503)
White Oak Conference Center, Silver Spring, Maryland
November 6, 2014

DRAFT QUESTIONS

NDA 206317
ferric pyrophosphate
APPLICANT: Rockwell Medical, Inc.

PROPOSED INDICATION: For the treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent stage 5 chronic kidney disease and to reduce the prescribed dose of erythropoiesis stimulating agent required to maintain desired hemoglobin levels.

Efficacy:
Ferric pyrophosphate is intended to treat iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent stage 5 chronic kidney disease (CKD). In the two pivotal studies conducted for this use, patients were randomized (1:1) to treatment with ferric pyrophosphate or placebo at each dialysis session for up to 48 weeks. Efficacy was assessed as the mean change in hemoglobin (Hgb) from baseline up to end-of treatment compared between the ferric pyrophosphate and placebo treatment groups. Results showed the following:

- Statistically significant difference between groups (ferric pyrophosphate better than placebo) for primary efficacy endpoint of mean change in hemoglobin from baseline to end-of-treatment.
    - SFP-4: 0.06 g/dL vs -0.3 g/dL for ferric pyrophosphate and placebo, respectively; p=0.01
    - SFP-5: -0.04 g/dL vs -0.39 g/dL for ferric pyrophosphate and placebo, respectively; p=0.01

Statistical issues were identified including: (1) Although treatment duration was planned for up to 48 weeks, only 18% of patients completed 48 weeks and 44% completed 24 weeks treatment; (2) Because the end of treatment Hgb values represent various time values, it is difficult to draw inferences about effects during the complete 48 weeks; (3) Differential reasons for treatment discontinuation could impact the magnitude of effect on Hgb level.

The applicant also asserts that the product reduces the prescribed dose of erythropoiesis stimulating agent (ESA) required to maintain desired hemoglobin levels. This claim is based on a single exploratory study (NIH-FP-01) which showed no significant difference between the

ferric pyrophosphate group and the placebo group in the mean percent change in prescribed ESA dose from baseline for the intent-to-treat (ITT) population (5.0% vs 37.3% for ferric pyrophosphate and placebo, respectively; p=0.052). Also, the mean percent change in actual ESA dose from baseline was not significantly different between the ferric pyrophosphate group and the placebo group in the ITT population (11.1% vs 40.7% for ferric pyrophosphate and placebo, respectively; p=0.111). Statistical issues were identified for this study including: (1) A single trial, no replication of the result; (2) No formal sample size or power calculations planned or conducted; and (3) Difficulty in the interpretation of the efficacy of ferric pyrophosphate over the placebo at the end of treatment.

Safety:
Observations from the safety evaluation in the pivotal trials in which 292 patients received ferric pyrophosphate and 296 received placebo include:

- More observed deaths in the ferric pyrophosphate treatment arm as compared to the placebo arm in both pivotal studies (SFP-4: 5 vs 3 for ferric pyrophosphate and placebo, respectively; SFP-5: 7 vs 3* for ferric pyrophosphate and placebo, respectively). [*one placebo patient was randomized but not treated].
- Overall deaths in the pivotal trials included 6 cardiac arrests and 4 sudden deaths in ferric pyrophosphate group and 2 cardiac arrests and 1 sudden death in placebo group.
- Hemodialysis (HD) vascular access thrombosis events observed in 5.1% of patients receiving ferric pyrophosphate and 3.7% of patients receiving placebo
- One patient with a suspected hypersensitivity event in the ferric pyrophosphate group and none in the placebo group.

Observations from the safety evaluation in the NIH-FP-01 trial (in which 54 patients received ferric pyrophosphate and 49 received placebo) include:

- 2 deaths in the ferric pyrophosphate group and 3 deaths in the placebo group

1. Ferric pyrophosphate is proposed for use for the treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent stage 5 chronic kidney disease (CKD 5HD).

   VOTE: Do the efficacy and safety results in Studies SFP-4 and SFP-5 support a positive benefit/risk for use of ferric pyrophosphate for any indication?

2. The applicant proposes to include in the label a claim that use of ferric pyrophosphate reduces the prescribed dose of erythropoiesis stimulating agent (ESA) required to maintain desired hemoglobin levels.

   DISCUSSION: Considering the limitations of the NIH-FP-01 study, should additional studies be required to establish efficacy of ferric pyrophosphate for this claim? Discuss important aspects of trial design for studies to substantiate clinical benefit for this use?